DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH INSTITUTE OF INFECTIOUS DISEASES
1425 PORTER STREET
FORT DETRICK, MARYLAND 21702-5011

REPLY TO ATTENTION OF:

March 22, 2005

Office of the Commander

Food & Drug Administration
Division of Dockets Management
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Dear Ladies and Gentlemen:

This letter is in reference to Docket Number 1980N-0280, Proposed Rule and Proposed Order: Bacterial Vaccines and Toxoids and provides supplementary information to section IV of the Proposed Rule and Proposed Order: Anthrax Vaccine Adsorbed – Proposed Order. We offer here a summation of the animal challenge experiments that supplement the human evidence for the effectiveness of anthrax vaccine adsorbed (AVA, BioThrax) as licensed in preventing anthrax infection, including infection by the inhalation route of exposure.

Rhesus macaques were vaccinated either via the subcutaneous (SC) or intramuscular (IM) route according to various dosing schedules (Table 1). The macaques received 0.5 ml of full-strength AVA (a human dose). New Zealand White (NZW) rabbits were vaccinated IM at either 0 and 2 weeks or 0 and 4 weeks (Table 2). The rabbits received 0.5 ml of either the full-strength vaccine (a human dose) or a 1:4 dilution of AVA.

After various periods of time, the vaccinated animals were exposed to a lethal spore aerosol, head-only for the nonhuman primates, in a dynamic aerosol chamber or muzzle-only (i.e., nose and mouth) for rabbits. The aerosol (with a mass median aerosol diameter of 1.2 μm) was generated by a three-jet Collison nebulizer. The exposures were 10 minutes long, and the aerosol was sampled continuously by an all-glass impinger (AGI-30; Ace Glass, Inc., Vineland, NJ). For each animal, the aerosol concentration of spores was calculated by plating out dilutions of a sample from the AGI onto tryptic soy agar plates (Difco, Detroit, MI). The inhaled doses were then determined (expressed as median lethal doses or LD_{50}). Aerosol LD_{50} values of 5.5×10^4 inhaled spores for the rhesus macaques and 1.1×10^5 inhaled spores for the NZW rabbits and was used. This means the macaques inhaled from 4 million to 55 million spores and the rabbits inhaled from 7 million to 300 million spores.

Outcomes of these inhalation-challenge vaccine-efficacy trials are presented in the tables attached. Overall, 95% of the vaccinated macaques survived 74 to 1005 times the median lethal dose of inhaled anthrax spores, whereas all of the unvaccinated macaques died. Overall, 98% of the vaccinated rabbits survived 63 to 2,742 times the median lethal dose of inhaled anthrax

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spores, whereas all the unvaccinated rabbits died. These results clearly demonstrate that the FDA-licensed anthrax vaccine adsorbed is effective in preventing inhalation anthrax in two animal models that the Institute of Medicine concluded are representative of the human form of inhalational anthrax.

The licensed regimen for AVA consists of three initial 0.5 ml doses given two weeks apart with three more doses 6, 12 and 18 months later. In these inhalation-challenge studies, only one or two doses of AVA were given to the animals, yet a high degree of protection resulted. In one study, seven of eight vaccinated macaques survived lethal inhalation challenge two years after vaccination. In the professional experience of our laboratory, the protective value of anthrax vaccine adsorbed in preventing inhalation anthrax is readily apparent.

If you have any questions about these data, my point of contact is Louise Pitt, PhD, Director, Center for Aerobiological Sciences at 301-619-4230.

Sincerely,

Erik A. Henchal
Colonel, U.S. Army
Commanding

Enclosures

Table 1: Protection of Rhesus macaques by the FDA-licensed anthrax vaccine adsorbed against lethal aerosol *B. anthracis* spore challenge **Corrected version, 28 March 2005**

# of AVA Doses	Vaccine Dose	Route of Vaccin-ation	Vaccination Schedule (weeks)	Challenge Point [a] (weeks)	Spore Challenge, Mean LD_{50}	Challenge *B. anthracis* Strain	Vac-cinated Survivors / Total	Unvac-cinated Survivors / Total	Journal Reference
2	0.5 ml	SC	0, 2	8	437	Ames	10 /10	0 / 5	1, 2
2	0.5 ml	SC	0, 2	38	203	Ames	3 / 3		1, 2
2	0.5 ml	SC	0, 2	100	330	Ames	7 / 8	0 / 2	1, 2
2	0.5 ml	IM	0, 4	16	899	Ames	9 / 9	0 / 2	3
2	0.5 ml	IM	0, 4	16	138 or 155	Ames	5 / 5	0 / 6	1
1	0.5 ml	IM	0	6	74	Ames	10 / 10	0 / 3	4
2	0.5 ml	IM	0, 4	10	398[b]	Namibia[c]	10 / 10	0 / 2	5
2	0.5 ml	IM	0, 4	10	1004[b]	Turkey[c]	8 / 10	0 / 2	5
				Overall			62 / 65 (95%)	0 / 22 (0%)	

SC: Subcutaneous injection
IM: Intramuscular injection
a - Weeks to challenge time is calculated from the first vaccine dose
b - LD_{50} challenges values for geographically diverse strains are "Ames LD_{50} equivalents"
c - Geographically diverse strains are designated by the country of origin

1 - Friedlander A, Pittman PR, Parker G. Anthrax vaccine: Evidence for safety and efficacy against inhalational anthrax. *Journal of the American Medical Association* 1999;282:2104-6. http://jama.ama-assn.org/cgi/reprint/282/22/2104.pdf
2 - Ivins BE, Fellows PF, Pitt MLM, Estep JE, Welkos SL, Worsham PL. Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol spore challenge in rhesus monkeys. *Salisbury Med Bull Supplement* 1996;87:125-126.
3 - Pitt MLM, Ivins BE, Estep JE, Farchaus J, Friedlander AM. Comparison of the efficacy of purified protective antigen and MDPH to protect non-human primates from inhalation anthrax. *Salisbury Med Bull Supplement* 1996;87:130.
4 - Ivins BE, Pitt MLM, Fellows PF, Farchaus JW, Benner GE, Waag DM, et al. Comparative efficacy of experimental anthrax vaccine candidates against inhalation anthrax in rhesus macaques. *Vaccine* 1998;16:1141-1148.
5 - Fellows PF, Linscott MK, Ivins BE, Pitt ML, Rossi CA, Gibbs PH, Friedlander AM. Efficacy of a human anthrax vaccine in guinea pigs, rabbits, and rhesus macaques against challenge by *Bacillus anthracis* isolates of diverse geographical origin. *Vaccine* 2001;19:3241-3247. Erratum in *Vaccine* 2001;20:635.

Table 2: Protection of New Zealand White rabbits by the FDA-licensed anthrax vaccine adsorbed against lethal aerosol *B. anthracis* spore challenge **Corrected version, 28 March 2005**

# of AVA Doses	Vaccine Dose	Route of Vaccin-ation	Vaccination Schedule (weeks)	Challenge Point [a] (weeks)	Spore Challenge Mean LD_{50}	Challenge *B. anthracis* Strain	Vac-cinated Survivors / Total	Unvac-cinated Survivors / Total	Journal Reference
2	0.5 ml	IM	0, 4	16	63	Ames	9 / 10	0 / 10	IOM, 7Apr01
2	0.5 ml	IM	0, 2	8	130	Ames	10 /10	0 / 8	IOM, 7Apr01
2	0.5 ml	IM	0, 4	10	133	Ames	8 / 8		6
2	¼ dilution	IM	0, 4	10	133	Ames	10 / 10		6
2	0.5 ml	IM	0, 4	10	84	Ames	10 /10	0 / 10	6
2	¼ dilution	IM	0, 4	10	84	Ames	10 / 10		6
2	0.5 ml	IM	0, 4	10	1305[b]	Namibia[c]	9 / 10	0 / 10	5
2	0.5 ml	IM	0, 4	10	1448[b]	India[c]	9 / 9	0 / 10	5
2	0.5 ml	IM	0, 4	10	360[b]	Norway[c]	9 / 10	0 / 10	5
2	0.5 ml	IM	0, 4	10	1191[b]	France[c]	10 / 10	0 / 10	5
2	0.5 ml	IM	0, 4	10	790[b]	Turkey[c]	10 / 10	0 / 10	5
2	0.5 ml	IM	0, 4	10	2743[b]	Indonesia[c]	10 / 10	0 / 10	5
				Overall			114 / 117 (98%)	0 / 88 (0%)	

IM: Intramuscular injection

a - Weeks to challenge time is calculated from the first vaccine dose

b - LD_{50} challenges values for geographically diverse strains are "Ames LD_{50} equivalents"

c - Geographically diverse strains are designated by the country of origin

5 - Fellows PF, Linscott MK, Ivins BE, Pitt ML, Rossi CA, Gibbs PH, Friedlander AM. Efficacy of a human anthrax vaccine in guinea pigs, rabbits, and rhesus macaques against challenge by *Bacillus anthracis* isolates of diverse geographical origin. *Vaccine* 2001;19:3241-3247. Erratum in *Vaccine* 2001;20:635.

6 - Pitt MLM, Little SF, Ivins BE, Fellows P, Barth J, Hewetson J, et al. In vitro correlation of immunity in a rabbit model of inhalational anthrax. *Vaccine* 2001;19:4768-4773. Also *J Applied Microbiology* 1999;87:304 (abstract).